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ScienceDirect
British Journal of Oral and Maxillofacial Surgery xxx (2017) xxx–xxx
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Clinicopathological features of squamous cell carcinoma of the oral cavity and oropharynx in young patients

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Abstract

Our aim was to examine the clinicopathological features of squamous cell carcinoma (SCC) of the oral cavity and oropharynx in a group of young patients who were dignosed during a 15-year period (2000–2014). Patients' clinical details, risk factors, and survival were obtained from medical records. Formalin-fixed, paraffin-embedded, tissue was tested for high-risk human papillomavirus (HPV). The results were compared with those of a matching group of older patients. We identified 91 patients who were younger than 45 years old, and the 50 youngest patients were studied in detail. The male:female ratio was 2:1, with more tumours located in the oral cavity than in the oropharynx (35 compared with 15). HPV-related SCC was restricted to the oropharynx. When matched for site, stage and HPV status, five-year overall survival was similar in young and matched older patients (log-rank test, $p = 0.515$). Our findings suggest that young patients with oral SCC have a disease profile similar to that of older patients with the condition. It is plausible that prognostic information generally available for oral cancers is applicable to young patients with the disease.

Keywords: Oral cancer; young patients; oropharyngeal; squamous cell carcinoma; human papillomavirus

Introduction

The profile of squamous cell carcinoma (SCC) of the head and neck has changed in recent decades, and in the UK there has been a steady increase in the number of SCC in the oral cavity and a dramatic increase in the incidence of oropharyngeal SCC.[1–3] Oncogenic human papillomavirus (HPV) is thought to account for the relatively recent increase in oropharyngeal SCC, with a contemporary study showing that 51.8% of oropharyngeal SCC diagnosed in the UK between 2002 and 2011 were HPV-positive.[4]

Trends in incidence seem to be age-related, and several studies have suggested that there is a higher incidence of HPV-related SCC in younger patients.[5,6] Overall, patients with HPV-related oropharyngeal SCC are 5–10 years younger than patients who are HPV-negative, and they are typically non-smokers who consume little alcohol. Patients with HPV-related oropharyngeal SCC have substantially better survival than those with HPV-negative tumours.[7] HPV testing is now recommended for all patients with oropharyngeal SCC and metastatic SCC in the head and neck when the site of the

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https://doi.org/10.1016/j.bjoms.2018.03.011

Please cite this article in press as: Martinez RC-P, et al. Clinicopathological features of squamous cell carcinoma of the oral cavity and oropharynx in young patients. *Br J Oral Maxillofac Surg* (2017), https://doi.org/10.1016/j.bjoms.2018.03.011

primary tumour is unknown.[8] In clinical practice, testing usually involves a combination of p16 immunohistochemistry and high-risk HPV DNA in situ hybridisation,[9] but other HPV-specific tests (such as polymerase chain reaction-based techniques) have also been validated.[10] There is evidence that these tests closely match the analytical reference test[10,11] and numerous studies have reported clinically relevant prognostic information.[12]

Though an earlier systematic review suggested that 23% of SCC of the oral cavity harbour HPV, these data are confounded by being drawn from studies that have used various different HPV test formats.[13] Contemporary studies that have used clinically recommended HPV tests indicate that only a small proportion (<5%) are associated with HPV infection.[14]

The aim of this study was to find out what the clinicopathological features of oral and oropharyngeal SCC were in a group of young patients, and compare their overall survival with that of a matched group of older patients.

Patients and methods

Patients and specimens

Patients were identified using the iLab pathology database at Newcastle-upon-Tyne Hospitals NHS Foundation Trust. The search strategy used SNOMED (Systematized Nomenclature of Medicine) coding to identify patients younger than 45 years old who had SCC of the oral cavity or oropharynx during the 15-year period (2000–2014). An older group of patients (over 45 years of age) who were matched for site, stage, and HPV status, was taken from existing databases.[15,16] Formalin-fixed, paraffin-embedded, blocks of tissue were retrieved for analysis. Clinicopathological features were obtained from medical records. Overall survival was calculated up to 60 months after the date of initial diagnosis. The study received ethics approval from the National Research Ethics Service Committee North East, Sunderland (REC reference: 11/NE/0118).

HPV testing

p16 immunochemical analysis: p16 immunohistochemical analysis was made using a proprietary kit (CINtec® Histology, Roche mtm laboratories AG, Germany) on a Ventana BenchMark Autostainer (Ventana Medical Systems Inc, USA). The p16 staining was considered "positive" when there was strong and diffuse nuclear and cytoplasmic staining present in more than 70% of the malignant cells.

High-risk HPV DNA in situ hybridisation: high risk HPV DNA in-situ hybridisation was done using proprietary reagents (INFORM® HPV III Family 16 Probe (B), Ventana Medical Systems Inc, USA) on a BenchMark Autostainer (Ventana Medical Systems Inc, USA). A "positive" result was defined as any blue reaction product that colocalised with the malignant cells.

High-risk HPV RNA in situ hybridisation: high-risk HPV mRNA was detected using the HPV RNAscope kit (Advanced Cell Diagnostics Inc, USA) according to the manufacturer's instructions. A "positive" result was defined as any staining that colocalised to the nucleus, or cytoplasm, or both, of malignant cells.

HPV genotyping

DNA was extracted from formalin-fixed, paraffin-embedded tissue using the cobas® DNA extraction kit (Roche Molecular Diagnostics Inc. USA). Samples were analysed using the automated cobas® HPV test on the cobas® 4800 instrument (Roche Molecular Systems Inc. USA). A "positive" result indicated the presence of HPV16, HPV18, or other high-risk HPV genotypes.

Statistical analysis

The data were pseudonymised, and the variables recorded were divided into demographic factors (age and sex), factors related to risk of SCC (relevant medical history, smoking habits, and alcohol consumption), clinical factors (site and staging of SCC, clinical outcome, and time to event) and HPV-related factors (p16 immunohistochemistry, high-risk HPV DNA in situ hybridisation, high-risk HPV RNA in situ hybridisation, and HPV genotyping). The information was collected on a standardised data-sheet and tabulated using Microsoft Excel 2003. Parametric and non-parametric statistical analyses were made with the help of IBM SPSS Statistics for Windows (version 21.0, IBM Corp, Armonk, NY, USA). Survival analyses were assessed using the log-rank (Mantel-Cox) test. Probabilities of less than 0.05 were accepted as significant.

Results

Clinical profile of young patients

Ninety-one patients aged under 45 years with oral or oropharyngeal SCC were identified. The distribution of the cases over five-year intervals is shown in Fig. 1. The youngest patient was 20 years old at the time of diagnosis and had dyskeratosis congenita. There were 42 patients 40 years old or less, and there were 49 between the ages of 41 and 44 years. The 50 youngest patients with sufficient material for HPV testing were studied in detail. The profile of these patients is shown in Table 1.

Data on tobacco use was available for only half the group. There were 18 smokers and seven who had never smoked. Of the smokers, four were heavy smokers (more than 20 cigarettes/day) and one claimed to smoke 80–100

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